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(54) Title
PHARMACEUTICAL COMPOSITIONS

(57) Claim

1. An oral pharmaceutical composition, which comprises (a) a therapeutically active substance, the bioavailability of which is improved by the presence of an absorption enhancing agent, (b) an effective amount of an absorption enhancing agent which comprises (i) a first ingredient selected from the group consisting of chenodeoxycholic acid, deoxycholic acid, and pharmaceutically acceptable salts of such acids, alone, or in combination with (ii) a second ingredient which in combination with (b)(i) synergistically improves the absorption still further, and (c) a pharmaceutically acceptable vehicle for (a) and (b).

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Complete Specification for the invention entitled:

Pharmaceutical Compositions

The following statement is a full description of this invention, including the best method of performing it known to me/us

RAN 4600/55

Abstract

Oral dosage forms comprising a therapeutic substance, for example, an antibiotic or insulin, an absorption enhancer for improving the bioavailability of the therapeutic substance, and a pharmaceutical vehicle are described. The absorption of the drug in the gastrointestinal tract is considerably improved by formulating it in combination with chenodeoxycholic or deoxycholic acids or, preferably, salts of these acids, and still further improved if a sucrose ester or glycerol ester is also employed as part of the absorption enhancer. This development enables the oral administration of drugs that are orally inactive due to poor absorption, as well as improvements in the absorption of drugs normally given by the oral route.

RAN 4600/55

This invention relates to orally administrable pharmaceutical compositions which contain chenodeoxycholic acid, or deoxycholic acid, or a salt of either of these acids, any of which may be used alone or in combination with a synergist, e.g. glycerides, to enhance the absorption of the therapeutic substance in the gastrointestinal tract.

In general, the administration of therapeutic substances can be accomplished in one of several different ways, the principal ones being oral, rectal and parenteral. Ideally, a drug should be capable of administration in any of these forms, as desired. In practice, however, many drugs, including a number of antibiotics, are not readily or sufficiently absorbed in the gastrointestinal tract, which for most purposes severely limits or precludes their utility in oral dosage forms. In the case of some therapeutic substances, such as sulfur drugs being used to treat mucosal inflammations, the lack of absorbability can be a benefit since it prolongs the exposure of the drug to the inflamed surface tissue. For most antibiotics as well as other drugs, however, absorption into the blood stream through the stomach or intestines is a required feature and administration as a tablet, pill or capsule provides greater convenience and, in some cases, physiological advantages.

The present invention provides, in one of its aspects, an orally administrable pharmaceutical composition comprising: (a) a therapeutically active substance, the bioavailability of which is improved by the presence of an absorption enhancing agent, an effective amount of (b) an absorption enhancing agent or agents (i) selected from the

group consisting of chenodeoxycholic acid, deoxycholic acid, and pharmaceutically acceptable salts thereof, alone, or together with (ii) a synergist for component (b)(i), and (c) a pharmaceutically acceptable vehicle for these ingredients.

Synergists for component (b)(i) which are useful as component (b)(ii) in compositions according to this invention are, generally, esters of fatty acids, including but not restricted to glycerol and sucrose esters. Preferably, component (b)(ii) is an ester of a medium chain, for example, C_8 to C_{12}, fatty acid. Especially favored for this invention are mono-, di- and triesters, for example, glycerides of medium chain fatty acids.

Another aspect of this invention is a method of therapeutic treatment which comprises orally administering to a warm blooded animal the above described readily absorbable pharmaceutical composition in an effective therapeutic amount.

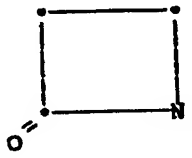
As will be developed more fully below, the invention is applicable to a broad spectrum of therapeutically active substances not normally administered by the oral route because of poor gastrointestinal tract absorption, as well as to therapeutic substances which are normally orally administrable but for which it is desired to improve the oral activity. Special mention is made of the family or class of materials known as beta-lactam antibiotics, a number of which are employed in the examples to illustrate the practice of the invention, and of insulin, which is also exemplified.

The compositions of this invention can be prepared as a solid, semi-solid or liquid into any of the various oral dosage forms, such as pills, tablets, capsules, powders, granules or beadlets, using standard or conventional methods and techniques.

The compositions can also be formulated or the oral dosage form modified for early or delayed release in the gastrointestinal tract, depending on therapeutic requirements. Thus, for instance, if it is desired that the active ingredient be released in the upper or lower intestine, rather than the stomach, the composition can be administered in the form of a pill, tablet, capsule or any other suitable delivery system.

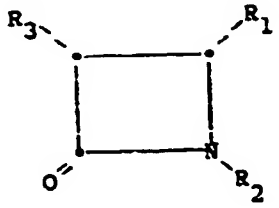
The described absorption enhancing agents are contemplated for use with a wide variety of therapeutic substances in accordance with the present invention, and in general with any therapeutic substance which is made orally more active by the presence of these absorption enhancers. Therapeutic substances utilizable in the practice of the invention can be selected from among, for example, retinoids, peptides, polypeptides, nutrient minerals (for example, salts of iron, calcium, potassium, zinc, etc.), proteins (for example, insulin), antibiotics (especially, the beta-lactams) and vitamins.

Among the most preferred materials for use as the therapeutic substance in the practice of this invention are beta-lactam antibiotics, particularly compounds having a beta-lactam ring as a central structure, that is, the structure

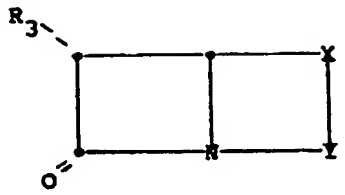


which can be substituted at various positions on the ring and/or fused with other ring systems which themselves can be substituted or unsubstituted. Some examples of well-known beta-lactam antibiotics include penicillins, cephalosporins and monocyclic beta-lactams.

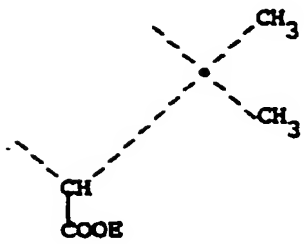
Especially favored beta-lactam antibiotics are those compounds of the formula



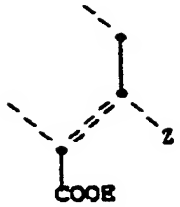
wherein R_1 is hydrogen or optionally substituted alkyl, R_2 is $SO_3^- M^+$, where M^+ is a proton or cation, R_3 is an acylamino group or hydroxyalkyl, or R_1 and R_2 together with the beta-lactam (azetidinone) ring to which they are bonded are



wherein X is S, O, SO, SO_2 or CH_2 and Y is the group



or



in which the carbon atom which carries the -COOE group is bonded to the nitrogen atom of the beta-lactam ring, Z is hydrogen, halogen, alkoxy or CH_2-T, T denotes hydrogen, alkyl -CO-O-, pyridinium, carboxamidopyridinium, aminopyridinium, carbamoyloxy, azido, cyano, hydroxyl, the group -S-phenyl which can be substituted or the group -S-het wherein het is an optionally substituted 5- or 6-membered heterocyclic ring, and E is hydrogen, a pharmaceutically usable ester group or salt-forming cation.

Especially preferred beta-lactam antibiotics and their pharmaceutically acceptable salts, esters and hydrates include ceftriaxone, a cephalosporin described for instance, in U.S. Patent No. 4,327,210; carumonam, a monocyclic beta-lactam described, for instance, in European Patent No. EP73063; piperacillin, a penicillin described for instance, in U.S. Patent No. 4,122,090; cefamandol, a cephalosporin described, for instance, in U.S. Patent No. 3,641,021; mezlocillin, a penicillin described, for instance, in U.S. Patent No. 3,974,142; cefazolin, a cephalosporin described, for instance, in U.S. Patent No. 3,516,997, all of the aforementioned disclosures of which are incorporated herein by reference. Also included are cefoxitin, amdinocillin, moxalactam, aztreonam, cefotaxime, cefmenoxine, ampicillin, cefoperazone, cefsulodine and thienamycin, all of which are known in the art.

The primary absorption enhancing agent used in this invention is, as mentioned, chenodeoxycholic acid or deoxycholic acid, or, preferably, a pharmaceutically acceptable salt of either one. The acids are readily available materials. The salts can be prepared by reacting either acid with a base having a non-toxic, pharmacologically and pharmaceutically acceptable cation. In general, any base which will form a salt with a carboxylic acid and whose pharmacological properties will not cause an adverse physiological effect when ingested by a warm-blooded animal

is considered as being within the scope of the invention. Suitable bases thus include, by way of illustration, alkali metal and alkaline earth metal hydroxides or carbonates, such as sodium hydroxide, potassium hydroxide, calcium hydroxide, potassium carbonate and the like; ammonia; primary, secondary and tertiary amines, such as monoalkyl amines, dialkylamines, trialkylamines; nitrogen-containing heterocyclic amines, such as piperidine; and basic amino acids, such as lysine, and the like. The pharmaceutically acceptable salts thus produced are the functional equivalent of the corresponding chenodeoxycholic or deoxycholic acids, and one skilled in the art will appreciate that, to the extent the salts are useful in therapy, the variety of salts encompassed by this invention are limited only by the criterion that the bases employed in forming the salts be both non-toxic and physiologically and pharmaceutically acceptable.

Preferably, though not necessarily, the above mentioned agent is used together with a second agent which synergistically improves the absorption still further and which preferably is a C_8 to C_{12} fatty acid mono-, di- or triglyceride or mixture of two or more such glycerides. Most preferred among these are mixtures containing a major amount, that is, more than 50 percent by weight, of a monoglyceride of a C_8 to C_{12} saturated fatty acid and minor amounts of a di- and/or triglyceride of a C_8 to C_{12} saturated fatty acid. Suitable materials are commercially available from Stokely-Van Camp, Inc., Columbus, Ohio, under the trade designated "CAPMUL" line of products.

Desired effective amounts of the absorption enhancing agent or agents, components (b)(i) and (b)(ii), in the composition will vary depending on such factors as the particular therapeutic substance being employed, the severity of the condition, the age of the subject being treated, and so forth, as the skilled practitioner will appreciate.

In general, for oral antibiotic compositions it is preferred to utilize from about 5 to about 1000 milligrams (mg), more preferably from about 50 to about 500 mg of each absorption enhancer used, for each unit dose of the composition. Such compositions will usually contain the beta-lactam antibiotic in amounts from about 25 to about 2500 mg, and more usually from about 100 to about 1500 mg, per unit dose.

Insulin-containing oral compositions in accordance with this invention will typically employ from about 5 to about 1000 mg, more usually from about 50 to about 500 mg of each absorption enhancer, with the insulin being present normally in amounts from about 0.1 to about 20,000 units, but more usually from about 1 to about 100 units, on a per unit dose basis.

The term "unit dose" is used here in the conventional sense to mean a single application or administration of the drug to the patient in the above stated amount.

As the vehicle any pharmaceutically acceptable solid, semi-solid or liquid carrier in which these components are soluble or readily dispersible can be used. Some examples are cocoa butter, polyethylene glycols, polypropylene glycols, glycerogelatine, methylcellulose, carboxymethyl-cellulose, and Suppocire® semi-synthetic bases (Gattefosse Corp., Elmsford, NY). Favored for this purpose are mixtures of triglycerides of C_{12} to C_{18} natural saturated fatty acids, preferably vegetable fatty acids having an even number of carbon atoms (C_{12}, C_{14}, C_{16}, etc.). Especially suitable are the pharmaceutical bases of Dynamit Nobel having the trade designation "WITEPSOL", some

appropriate examples of which are listed below:

WITEPSOL E75 (m.p. 37-39°C, OH value 220-230)
WITEPSOL E76 (m.p. 37-39°C, OH value 30-40)
WITEPSOL E79 (m.p. 36-38°C, OH value 25-35)
WITEPSOL E85 (m.p. 42-44°C, OH value 15 max.)
WITEPSOL H5 (m.p. 34-36°C, OH value 5 max.)
WITEPSOL H12 (m.p. 32-33.5°C, OH value 15 max.)
WITEPSOL H15 (m.p. 33.5-35.5°C, OH value 15 max.)
WITEPSOL H19 (m.p. 33.5°C, OH value 20-30)
WITEPSOL S52 (m.p. 32-33.5°C, OH value 50-65)
WITEPSOL S55 (m.p. 33.5-35.5°C, OH value 50-65)
WITEPSOL S58 (m.p. 32-33.5°C, OH value 60-70)
WITESPOL W25 (m.p. 33.5-35.5°C, OH value 20-30)
WITESPOL W31 (m.p.. 35-37°C, OH value 25-35)
WITESPOL W35 (m.p. 33.5-35.5°C, OH value 40-50)
WITEPSOL W45 (m.p. 33.5-35.5°C, OH value 40-50)

Amounts for component (c) will generally be those which are conventional for pharmaceutical carrier materials, in amounts which can be reasonably and safely administered.

While the invention is described in greatest detail with respect to beta-lactam antibiotics, it is again emphasized that the invention is contemplated as being applicable to other therapeutically useful substances, whether naturally occurring, or semi-synthetically or synthetically produced. Thus, for instance, it is conceived, and demonstrated herein, that the gastrointestinal absorption of the bio-compatible proteinaceous material insulin, which in the usual case can be administered to satisfactory effect only parenterally, is enhanced by means of the described invention.

The preferred method of administering the therapeutic substance, for instance, the beta-lactam antibiotic, together with one or both absorption enhancers is in the form of an enteric coated entity, that is, as an enteric coated solid

dosage form. The vehicles can be in either solid or liquid form and can be filled into hard- or soft-shell capsules, or the liquid vehicle can be absorbed on a suitable carrier to make a free flowing powder and then filled into the capsule or, alternatively, compressed into pills or tablets. Other dosage forms can include non-enteric coated delivery systems, that is, capsules or tablets, in which the antibiotic and absorption enhancer are themselves enteric coated, for example, in the form of micro encapsulated beadlets which are loaded into a hard- or soft-shell capsule or which may be compressed into a tablet. Still other possible dosage forms include enteric coated microcapsule or beadlet forms of the antibiotic or other therapeutic substance or drug mixed with an absorption enhancer which may thereafter be encapsulated in an enteric or non-enteric coated capsule.

Usage of enteric coating materials in the manner described above will serve to protect the beta-lactam antibiotic or other susceptible therapeutic substance from the gastric fluid and to achieve optimum delivery of the therapeutic substance and absorption enhancer to the intestine.

The efficacy of particular enteric coating materials can be measured using known USP methods. Merely by way of illustration, suitable enteric coating materials for purposes of this invention include the following:

cellulose acetate phthalate
hydroxypropyl methylcellulose phthalate
polyvinyl acetate phthalate
methacrylic acid
methacrylic acid esters

These enteric coating materials may be applied with or without plasticizers, such as acetylated glycerides or diethylphthalate, using methods known to those skilled in the art, some of which are illustrated further below.

The percentage of enteric coating applied is usually between about 1 and about 10 percent by weight, or more, and most desirably from about 2 to about 8 percent by weight, based on the total capsule or tablet weight. Examples of suitable enteric coating formulations are given below.

Enteric Coating Formulations

Ingredients	% w/w
Solution A:	
Hydroxypropyl methylcellulose phthalate (HPMCP)	5.0
Triacetin	0.5
Methylene chloride	47.25
Denatured alcohol	47.25
Solution B:	
HPMCP	10.0
Titanium dioxide	0.2
Dimethyl polysiloxane	0.05
Acetone	44.875
Denatured alcohol	44.875

Solution C:

Cellulose acetate phthalate (CAP)	8.5
Diethyl phthalate	1.5
Titanium dioxide	0.2
Acetone	44.9
Denatured alcohol	44.9

Solution D:

Polyvinyl acetate phthalate	5.0
Acetylated glycerides	0.8
Methylene chloride	47.1
Denatured alcohol	47.1

Solution E:

Methacrylic acid or methacrylic acid ester (Eudragit S or L, Rohm Pharma, GMBH, Wetterstadt, West Germany)	8.0
Acetone	46.0
Anhydrous alcohol	46.0
Plasticizer	q.s.

Compositions in accordance with this invention can be formulated to contain, in addition, the usual amounts of additives or supplementary ingredients, which may be selected from among conventional materials for pharmaceutical compositions. Examples include thickening agents, such as silicic acid (for instance, the trade designated "Aerosil" products); bentonites; colloidal clay; carboxymethyl celluloses; modified montmorillonites, such as alkyl ammonium salts of montmorillonites (for instance, the commercial products known as "Bentone"); organic thickening and structure-forming agents, such as saturated higher fatty acids and alcohols containing from 12 to 20 carbon atoms (for

instance, stearic or palmitic acids, or stearic or cetyl alcohol); waxes; spermaceti; monoglycerides of saturated or unsaturated higher fatty acids such as stearic acid, palmitic acid or oleic acid; gelling agents, such as aluminum stearate; dispersing agents, such as anionic, non-ionic or cationic surfactants; emulsifying agents, such as lecithin, and so forth.

The compositions can also contain pharmaceutically acceptable adjuvants, such as binders or lubricants for tableting, stabilizing agents, antioxidants, flavoring agents, preservatives, coloring agents and buffering agents, selected from among materials known for such purposes.

In vivo tests were utilized to evaluate the enhanced absorption of orally administrable drug formulations in accordance with the present invention.

A first in vivo test protocol was as follows: two species of test subjects (humans and rats) were utilized, with dosing of ß-lactam antibiotic by the oral and enteral routes for both species. For oral administration the antibiotics were prepared in distilled water or in a vehicle, such as Witepsol H15, alone, or together with CAPMUL MCM 90, and an absorption enhancer, such as sodium chenodeoxycholate (NaCDC) or its acid form, chenodeoxycholic acid, or sodium deoxycholate (NaDC) or its acid form, deoxycholic acid. Enterally the antibiotics were prepared in the same way and the mixtures were given in the duodenal area.

Plasma levels of the antibiotics prepared in the various formulations following these routes of administration were measured by withdrawing blood from the arm of the human and from the tail vein of the rat and centrifuging immediately. The antibiotic-containing blood samples from the rats were analyzed by bioassay on a Nunc plate; E. coli 1346 grown overnight on an antibiotic agar #1 slant was washed with

saline to give a suspension with 90% transmittance on a Bausch and Lomb Spectronic 20 (650 nm), sixteen milliliters (ml) of the resulting suspension were added to 600 ml of molten antibiotic agar #1, two hundred ml of the seeded agar were poured into each Nunc plate (243 x 243 x 18 mm), and agar wells were punched and removed from the agar plate so that 20 microliters (µl) of the sample could be added to each well. In the case of ceftriaxone, acetonitrile was used to deproteinize the sample prior to assay.

The antibiotic-containing blood samples from the humans were analyzed by the HPLC analytical method described by I.H. Patel, et al., "Multiple Intravenous Dose Pharmacocinetics of Ceftriaxone in Man", Chemotherapy 27 (Suppl. 1): 47-56 (1981), page 49, incorporated herin by reference.

The data in the form of blood levels of antibiotic in micrograms per milliliter (µg/ml) and percent bioavailability in humans and rats following the specified dose of the antibiotic in water or with enhancer are set forth in the following Table (Table 1).

The Table indicates that significantly higher levels of ceftriaxone, cefamandole, carumonam, amdinocillin, moxalactam and thienamycin are obtained when these antibiotics are prepared in sodium chenodeoxycholate rather than in water. The level of ceftriaxone is also increased by the use of sodium deoxycholate, as shown. The Table also indicates that absorption of ceftriaxone is synergistically enhanced by the use of CAPMUL MCM 90.

TABLE 1

BLOOD LEVELS OF ANTIBIOTICS

No.	Formulation	Species	% Bioavailability	Cmax (µg/ml)
1)*	Ceftriaxone (1.5 g) Witepsol H15 (2.95g)	human	less than 1	1.55
2)	Ceftriaxone (1.5g) NaCDC (0.25g) Witepsol H15 (2.95g)	human	approx. 5	10.7
3)	Ceftriaxone (1.0g) NaCDC (0.25g) CAPMUL MCM 90(0.75g) Witepsol H15 (1.8g)	human	approx. 10	12.8
4)*	Ceftriaxone (6 mg) Water (0.5 ml)	rat	3.4	2.0
5)	Ceftriaxone (6 mg) NaCDC (2.5 mg) Water (0.5 ml)	rat	28.1	23.5
6)*	Ceftriaxone (6 mg) Witepsol H15 (14 mg)	rat	4.5	2.5
7)	Ceftriaxone (6 mg) NaCDC (2.5 mg) WitepsolH15 (11.5 mg)	rat	28.0	27.0

TABLE 1

BLOOD LEVELS OF ANTIBIOTICS

No.	Formulation		Species	% Bioavailability	Cmax (µg/ml)
8)	Ceftriaxone	(6 mg)	rat	4.5	5.6
	CAPMUL MCM 90	(10µl)			
	Water	(0.5 ml)			
9)	Ceftriaxone	(6 mg)	rat	43.0	46.0
	NaCDC	(2.5 mg)			
	CAPMUL MCM 90	(10 µl)			
	Water	(0.5 ml)			
10)	Ceftriaxone	(6 mg)	rat	23.7	22.7
	NaDC	(2.5mg)			
	Water	(0.5 ml)			
11)*	Cefamandole	(5 mg)	rat	7.0	1.3
	Water	(0.5 ml)			
2)	Cefamandole	(5 mg)	rat	39.5	11.3
	NaCDC	(2.5 mg)			
	Water	(0.5 ml)			

TABLE 1

BLOOD LEVELS OF ANTIBIOTICS

No.	Formulation		Species	% Bioavailability	Cmax (µg/ml)
13)*	Carumonam Water	(5 mg) (0.5 ml)	rat	0.0	0.0
14)	Carumonam NaCDC Water	(5 mg) (2.5 mg) (0.5 ml)	rat	15.9	2.0
15)*	Amdinocillin Water	(5 mg) (0.5 ml)	rat	6.0	0.7
16)	Amdinocillin NaCDC Water	(5 mg) (2.5 mg) (0.5 ml)	rat	37.0	6.8
17)*	Moxalactam Water	(5 mg) (0.5 ml)	rat	0.0	0.0
18)	Moxalactam NaCDC Water	(5 mg) (2.5 mg) (0.5 ml)	rat	16.2	3.7
19)*	Thienamycin Water	(5 mg) (0.5 ml)	rat	0.0	0.0

TABLE 1

BLOOD LEVELS OF ANTIBIOTICS

No.	Formulation		Species	% Bioavailability	Cmax (µg/ml)
20)	Thienamycin	(5 mg)	rat	100.0	52.0
	NaCDC	(10.0 mg)			
	Water	(0.5 ml)			

* control or comparison formulation

In addition, an in vivo test was utilized to evaluate the enhanced absorption of orally administered insulin formulations which are also in accordance with the present invention.

In this test protocol, rats were fasted overnight, anesthetized and drug administration was carried out internally by injection into the duodenum. Blood samples were collected on chemically pretreated paper (Chemistrip bg, Boehringer Mannheim Diagnostics, Inc., Baltimore, MD) by tail bleeding at various time intervals, and the glucose level was measured by reading on an Accucheck bg blood glucose monitor (Biodynamics, Baltimore, MD).

The following formulations were thus administered:

Insulin Formulations:

1)	Water	0.5 ml
	Insulin	0 units
	NaCDC	0 mg
2)	Water	0.5 ml
	Insulin	10 units
	NaCDC	0 mg
3)	Water	0.5 ml
	Insulin	10 units
	NaCDC	2.5 mg
4)	Water	0.5 ml
	Insulin	20 units
	NaCDC	0 mg
5)	Water	0.5 ml
	Insulin	20 units
	NaCDC	2.5 mg

The data in the form of blood glucose levels in mg/dl (mg%) in the rats at various time intervals following a 10 or 20 unit dose of the insulin in water or with enhancer are set forth in the following Table.

As can be seen, the presence of sodium chenodeoxycholate (NaCDC) in the formulations resulted in a significant temporary lowering of blood sugar, which is indicative of enhanced insulin uptake induced by NaCDC. The initial rise in the blood glucose level in response to anesthesia and surgery was expected.

TABLE 2

SUMMARY OF INSULIN EFFECTS ON BLOOD GLUCOSE, WITH AND WITHOUT ENHANCER (RATS)

	Blood Glucose Levels, mg/dl				
	Formulation				
Time (min.)	No. 1 (H_2O)	No. 2 Insulin 10	No. 3 Insulin 10 + NaCDC	No. 4 Insulin 20	No. 5 Insulin 20 + NaCDC
at anesthesia	67.5	74.0	74.0	82.5	73.5
at injection	99.0	95.3	106.0	117.0	115.0
15	83.2	83.0	84.6	94.5	73.0
30	77.5	80.5	52.0	95.0	47.0
60	73.0	81.8	57.0	90.0	38.5
90	81.0	72.5	68.0	80.3	43.8
120	71.0	65.5	64.6	82.5	43.5
150	69.5	73.0	76.0	92.8	67.8

In the foregoing tests, solutions of the drugs were prepared by dissolving the drug in distilled water with stirring at room temperature and, if the enhancer was present, adding the enhancer in particulate form slowly with continued stirring to form a finely divided suspension..

Below is a procedure which can be used to prepare an orally administrable drug composition of this invention in the particular form of soft gelatin capsules.

Batch Method - Soft Gelatin Capsules (10,000 Units)

Ten thousand (10,000) grams of ceftriaxone and 2,500 grams of sodium deoxycholate are blended at room temperature in a roll mixer. In a separate container made of stainless steel, 17,500 grams of Witepsol H15 are melted by warming gently at 40-50°C. The blend of ceftriaxone and sodium deoxycholate is added slowly to the melted Witepsol and mixed well to form a homogeneous dispersion. Seventy-five hundred (7,500) grams of Capmul MCM 90 are added to this dispersion and mixed well to provide homogeneity. The resulting dispersion is deaerated, then brought to a temperature of 40°C. Using a standard soft gelatin encapsulating machine, the dispersion is loaded into soft gelatin capsules (10,000 in number). After an appropriate drying cycle, these capsules may be enteric coated using standard procedures, such as those which have been described above.

Particular formulations for various antibiotics and for insulin are now illustrated.

Example 1

Ingredients	mg / unit dose		
	25 mg	500 mg	1000 mg
Drug e.g., Ceftriaxone, Cefamandol, Cefazolin, Cefoxitin, Carumonam, Aztreonam, Amdinocillin, Moxalactam, Cefotaxime, Piperacillin, Mezclocillin,			

(6R,7R)-7-[(Z)-2-(2-amino-4-thiazolyl)-2-(methoxy-imino)acetamido]-3-[(5-methyl-2H-1,2,3,4-tetrazol-2-yl)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt Cefmenoxime, Cefoperazone, Cefsulodine, Thienamycin	25 mg	500 mg	1000 mg
Sodium chenodeoxycholate	250 mg	250 mg	250 mg
Witepsol H15, q.s.	1000 mg	2000 mg	3000 mg
Total	1000 mg	2000 mg	3000 mg

The following example illustrates oral dosage forms of the invention in which two absorption enhancing additives are used in combination. In these Capmul MCM 90 is a saturated fatty acid glyceride mixture containing about 90% monoglycerides in the C_8-C_{10} range.

Example 2

	mg / unit dose		
Ingredients	25 mg	500 mg	1000 mg
Drug, e.g. Ceftriaxone Cefamandol, Cefazolin, Cefoxitin, Carumonam, Aztreonam, Amdinocillin, Moxalactam, Cefotaxime, Piperacillin, Mezclocillin, (6R,7R)-7-[(Z)-2-(2-amino-4-thiazolyl)-2-(methoxy-imino)acetamido]-3-[(5-methyl-2H-1,2,3,4-tetrazol-2-yl)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt Cefmenoxime, Cefoperazone, Cefsulodine, Thienamycin	25 mg	500 mg	1000 mg

Sodium chenodeoxy-cholate	250 mg	250 mg	250 mg
Capmul MCM 90	750 mg	750 mg	750 mg
Witepsol H15, q.s.	2000 mg	3000 mg	4000 mg
Total	2000 mg	3000 mg	4000 mg

~~WHAT IS CLAIMED:~~
The claims defining the invention are as follows:

1. An oral pharmaceutical composition, which comprises (a) a therapeutically active substance, the bioavailability of which is improved by the presence of an absorption enhancing agent, (b) an effective amount of an absorption enhancing agent which comprises (i) a first ingredient selected from the group consisting of chenodeoxycholic acid, deoxycholic acid, and pharmaceutically acceptable salts of such acids, alone, or in combination with (ii) a second ingredient which in combination with (b)(i) synergistically improves the absorption still further, and (c) a pharmaceutically acceptable vehicle for (a) and (b).

2. A composition in accordance with claim 1, wherein the composition is in the form of a solid, semi-solid or liquid.

3. A composition in accordance with claim 2, wherein the composition is a solid, with or without an enteric coating.

4. A composition in accordance with claim 1, wherein the therapeutically active substance is selected from the group consisting of antibiotics, retinoids, peptides, polypeptides, proteins, vitamins, and nutrient minerals.

5. A composition in accordance with claim 4, wherein the therapeutically active substance is a beta-lactam antibiotic.

6. A composition in accordance with claim 5, wherein the beta-lactam antibiotic is selected from the group consisting of ceftriaxone, cefamandol, cefazolin, cefoxitin, carumonam, aztreonam, amdinocillin, moxalactam, cefotaxime, piperacillin, mezlocillin, cefmenoxime, cefoperazone, cefsulodine and thienamycin.

7. A composition in accordance with claim 1, wherein the therapeutically active substance is a protein.

8. A composition in accordance with claim 7, wherein the therapeutically active substance is insulin.

9. A composition in accordance with claim 1, in which component (b)(i) is a salt of chenodeoxycholic acid.

10. A composition in accordance with claim 9, in which component (b)(i) is sodium chenodeoxycholate.

11. A composition in accordance with claim 1, in which component (b)(i) is a salt of deoxycholic acid.

12. A composition in accordance with claim 11, in which component (b)(i) is sodium deoxycholate.

13. A composition in accordance with claim 1, in which component (b)(i) is an ester of a fatty acid.

14. A composition in accordance with claim 13, in which component (b)(ii) is a glycerol or sucrose ester.

15. A composition in accordance with claim 14, in which component (b)(ii) is a monoglyceride, or diglyceride or triglyceride of a medium chain fatty acid, or a mixture of two or more of any of the foregoing.

16. A composition in accordance with claim 15, in which the absorption enhancing agent comprises sodium deoxycholate and glycerides of a C_8-C_{10} fatty acid.

17. A composition in accordance with claim 1, which contains from about 25 to about 2500 milligrams of a beta-lactam antibiotic, and from about 5 to about 1000 milligrams of an absorption enhancer or enhancers, per unit

dose.

18. A composition in accordance with claim 17, which contains from about 100 to about 1500 milligrams of the beta-lactam antibiotic, and from about 50 to about 500 milligrams of the absorption enhancer or enhancers, per unit dose.

19. A composition in accordance with claim 1, which contains from about 0.1 to about 20,000 units of insulin, and from about 5 to about 1000 milligrams of absorption enhancer or enhancers, per unit dose.

20. A composition in accordance with claim 19, which contains from about 1 to about 100 units of insulin, and from about 50 to about 500 milligrams of absorption enhancer or enhancers.

21. A composition in accordance with claim 1, in which the composition is in the form of a pill, tablet or capsule.

22. A composition in accordance with claim 21, which is in the form of a soft gelatin capsule.

23. A composition in accordance with claim 22, in which the soft gelatin capsule is enteric coated.

24. A method for orally administering a therapeutically active substance, the absorption of which is enhanced by the presence of an absorption enhancing agent, which comprises orally administering a composition comprising (a) the therapeutically active substance, (b) an effective amount of an absorption enhancing agent which comprises (i) a first ingredient selected from the group consisting of chenodeoxycholic acid, deoxycholic acid, and pharmaceutically acceptable salts of such acids, alone, or in combination with (ii) a second ingredient which together with (b)(i) synegistically

improves the absorption still further, and (c) a pharmaceutically acceptable vehicle for (a) and (b).

25. A method in accordance with claim 24, in which the composition is in the form of a solid, semi-solid, or liquid.

26. A method in accordance with claim 25, in which the composition is a solid, with or without an enteric coating.

27. A method in accordance with claim 24, in which the therapeutically active substance is selected from the group consisting of antibiotics, nutrient minerals, retinoids, peptides, polypeptides, proteins, and vitamins.

28. A method in accordance with claim 27, in which the therapeutically active substance is a beta-lactam antibiotic.

29. A method in accordance with claim 28, in which the therapeutically active substance is a beta-lactam antibiotic selected from the group consisting of ceftriaxone, cefamandol, cefazolin, cefoxitin, carumonam, aztreonam, amdinocillin, moxalactam, cefotaxime, piperacillin, mezlocillin, cefmenoxime, cefoperazone, cefsulodine and thienamycin.

30. A method in accordance with claim 24, in which the therapeutically active substance is a protein.

31. A method in accordance with claim 30, in which the therapeutically active substance is insulin.

32. A method in accordance with claim 24, in which the absorption enhancing agent is a salt of chenodeoxycholic acid.

33. A method in accordance with claim 24, in which the absorption enhancing agent comprises sodium chenodeoxycholate together with glycerides of a C_8-C_{10} fatty acid.

34. The novel compositions and methods substantially as described hereinbefore.

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